Original Article

Use of GeneXpert *Mycobacterium tuberculosis*/rifampicin for rapid detection of rifampicin resistant *Mycobacterium tuberculosis* strains of clinically suspected multi-drug resistance tuberculosis cases

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Background: Multi-drug resistance (MDR) TB is defined as tuberculosis (TB) disease caused by a strain of *Mycobacterium tuberculosis* (MTB) that was resistant to at least isoniazid and rifampicin (RIF). Emerging Multidrug-Resistant TB is one of the major concerns of health policy and rapid detection of *M. tuberculosis* and detection of RIF resistance in infected patients are essential for disease management. The aim of this study was to evaluate patterns of RIF resistance in cases of sputum positive pulmonary TB by using GeneXpert MTB/RIF and comparing between phenotypic and genotypic testing of RIF resistance in MTB strains of clinically suspected MDR-TB isolated cases in western Algeria.

Methods: In this study 50 sputum positive cases of pulmonary TB who were potential MDR suspect were included. Their sputum samples were collected and subjected to sputum smear microscopy, culture and conventional MTB/RIF test followed by GeneXpert MTB/RIF assay.

Results: Of total 50 cases included in this study, MTB was detected in all patients (100%) by GeneXpert MTB/RIF. However, RIF's resistance was detected in only 21 cases (42%) by GeneXpert MTB/RIF. All RIF resistant strains detected by GeneXpert MTB/RIF were phenotypically confirmed as MDR strains. 42.85% of cases were retreatment failure cases, retreatment cases smear positive at 4 months were 23.82%. While 19.05% of cases were retreatment cases smear positive at diagnosis, and 14.28% patient had history of contact with MDR-TB. Sensitivity, specificity, positive predictive value and negative predictive value of Xpert MTB/RIF to detect RIF resistance in comparison to conventional phenotypic drug susceptibility technique were found equal to the rates of 100%, 100%, 100% and 100%, respectively.

Conclusions: GeneXpert MTB/RIF assay is efficient and reliable technique for the rapid diagnostic of TB. It's simplicity, high sensitivity and specificity for RIF resistance detection make this technique a very attractive tool for diagnostic of MTB and RIF resistance in MDR cases.

Keywords: *Mycobacterium tuberculosis* (MTB); rifampicin resistance; multi-drug resistance (MDR); GeneXpert MTB/RIF

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Introduction

Tuberculosis (TB) is the most common infectious disease worldwide caused by *Mycobacterium tuberculosis* (MTB).

In the global TB report [2014], WHO reported that in 2013, nine million people developed TB. At the same time, global burden of multidrug-resistant TB (MDR-TB) was estimated to be 480,000 cases leading to estimated 210,000 deaths (1). In Africa, 1.9% of new cases and 9.4% of diagnosed and treated patients are infected by an MDR strain (2). Multi-drug resistance (MDR) TB is defined as TB disease caused by a strain of *M. tuberculosis* that was resistant to at least isoniazid and rifampicin (RIF) (3). Emerging Multidrug-Resistant Tuberculosis-TB is one of the major concerns of health policy (4). Currently, less than 10% of multi-drug resistant tuberculosis (MDR-TB) cases in the world are detected (5). The rapid detection of *M. tuberculosis* in infected patients is essential for disease management (6). During the past few years, molecular methods have been developed to identify drug resistance causing gene muta-tions (7,8). One of the latest techniques is GeneXpert MTB/RIF, which can detect mutations in the *rpoB* gene only; due to close association of RIF resistance and MDR TB, this technique has been used to detect MDR TB cases (9). The technique has been thoroughly evaluated (10) and used in many countries (11). It has a sensitivity and specificity of 90.4% and 98.4%, respectively (12,13).

Culture is the "gold standard" for final determination, but it is time consuming and may take up 2 till 8 weeks (6). Molecular tests dramatically shorten diagnosis time from months to days (MTBDRplus) or even hours (GeneXpert MTB/RIF).The assay can generally be completed in less than 2 hours (14,15).

The objectives of this study were to use cartridge based nucleic acid amplification testing to evaluate patterns of RIF resistance in cases of sputum positive pulmonary TB and compare between phenotypic and genotypic testing of RIF resistance in MTB strains of clinically suspected MDR-TB isolated cases in western Algeria.

Methods

A prospective study was conducted at pneumophtisiology department (B) at Oran hospital (western Algeria) along the period of 2013 to 2014. The material of study came from different hospital centers and different public health sectors of western Algeria. Fifty clinically suspected MDR-TB cases were selected. An absolute confidentiality of the patients' vital information was maintained for ethical purposes and an ethical approval was obtained from the institution in which the study was carried out.

The following variables were collected through an administered questionnaire during sputum collection: sex, age, treatment history (new or previously treated). Inclusion criteria used for MDR suspect consist of retreatment failure, retreatment cases sputum positive at 4 months, contact of known MDR-TB case, sputum positive retreatment case at diagnosis.

After identifying potential MDR-TB suspect cases, three sputum samples were collected from each patient. One specimen was used for direct microscopic examination by Ziehl-Neelsen method, one specimen was processed with N-acetyl-L-cysteine and sodium hydroxide before solid culture, and MTB/RIF test. The last specimen was used for direct testing with the Xpert MTB/RIF test. Xpert MTB/RIF assay was compared with conventional culture method for detecting TB and with conventional phenotypic drug susceptibility testing for detecting RIF's resistance. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

Phenotypic drug susceptibility testing

Cultures obtained on Lowenstein-Jensen medium were collected and tested for drug susceptibility to RIF, isoniazid, ethambutol and streptomycin. Drug susceptibility testing was performed using the proportional method with Lowenstein-Jensen medium. The critical drug concentrations were 0.2 µg/mL for isoniazid, 40 µg/mL for RIF, 2 µg/mL for ethambutol and 4 µg/mL for streptomycin. The critical proportion of resistant bacillus necessary to define a resistant strain is 1% for the four tested drugs (15).

Genotypic drug susceptibility testing

For each of the samples; unscrew lid of sputum collection container; add Sample Reagent 2:1 (v/v) to the sample,

Table 1 Rifampicin sensitivity pattern

Sex	Rifampicin		Total (%)	P value
	Rifampicin resistant (%)	Rifampicin sensitive (%)		
Male	15 (42.9)	20 (57.1)	35 (100.0)	0.8
Female	6 (40.0)	9 (60.0)	15 (100.0)	
Total	21 (42.0)	29 (58.0)	50 (100.0)	

Table 2 Distribution of Rifampicin resistant cases according to patients' category

Category	Number of cases	Percentage (%)
Retreatment failure	9	42.85
Retreatment cases sputum positive at 4 months	5	23.82
Contact of known MDR-TB case	4	14.28
Sputum positive retreatment case at diagnosis	3	19.05
Total	21	100

MDR-TB, multi-drug resistant tuberculosis.

replace the lid, and shake vigorously 10–20 times. Incubate for 15 minutes at room temperature. At one point between 5 and 10 minutes of the incubation again shake the specimen vigorously 10–20 times. Samples should be liquefied with no visible clumps of sputum. Particulate matter may exist that is not part of the sample. At least 2 mL of processed sample was taken with the plastic transfer pipette from the collection container to the single-use, disposable, self-contained GeneXpert cartridge. Then it was subjected to GeneXpert® MTB/RIF to create a test. Results were noted after 2 hours.

Results

In this study, 50 clinically suspected MDR-TB cases were selected and their sputum samples were tested by phenotypic drug susceptibility methods and genotypic drug susceptibility methods using the test GeneXpert MTB/RIF.

Of total 50 cases included in this study, MTB was detected in all patients (100%) by GeneXpert MTB/RIF.

Table 3 Prevalence of multi-drug resistant tuberculosis (MDR-TB)

Xpert MTB/RIF	DST			MDR-TB	P value
	RIF resistant	RIF sensitive	Isoniazid resistant		
RIF resistance detected	21	0	21	21	0.001
RIF resistance not detected	0	29	0	0	
Total	21 (100%)	29 (100%)	21 (100%)	21 (100%)	

MTB, *Mycobacterium tuberculosis*; DST, drug susceptibility testing; RIF, rifampicin.

However, RIF's resistance was detected in only 21 cases (42%) by GeneXpert MTB/RIF. Gender distribution showed that 15 (71.43%) were male and 6 (28.57%) were female among RIF resistant cases (*Table 1*).The sex ratio was of 2.5. The distribution according to age showed that the majority of patients with RIF resistance belonged to age group of 31–40 years (n=10; 47.62%) followed by 21–30 and 41–50 years with (n=4; 19.04%) for each age group and 51–60 years with (n=3; 14.28%).

Table 1 shows that 15 (42.9%) male out of 35 and 6 (40.0%) female out of 15 were resistant to RIF, while 20 (57.1%) male out of 35 and 9 (60.0%) female out of 15 were sensitive to it.

42.85% of cases were retreatment failure cases, retreatment cases smear positive at 4 months were 23.82%. While 19.05% of cases were retreatment cases smear positive at diagnosis, and 14.28% patient had history of contact with MDR-TB (*Table 2*).

Comparison of phenotypic and genotypic resistance drug susceptibility showed that all strains harboring mutations in *rpoB* were phenotypically resistant to RIF and isoniazid. Our results show that all RIF resistant strains detected by GeneXpert *MTB*/RIF were phenotypically confirmed as MDR strains (*Table 3*).

Twenty one cases were identified as being RIF resistant MTB by the conventional method. On comparing this with Xpert MTB/RIF; we noted a total of twenty one cases that are RIF resistant MTB. Sensitivity, specificity, positive predictive value and negative predictive value of Xpert MTB/RIF to detect RIF resistance in comparison to conventional phenotypic drug susceptibility technique were

Table 4 Performance characteristics of the Xpert MTB/RIF assay compared to drug susceptibility testing for rifampicin (RIF)

Xpert MTB/RIF	DST		PPV	NPV
	RIF resistant	RIF sensitive		
RIF resistance detected	21	0	100%	
RIF resistance not detected	0	29		100%
Sensitivity	100%			
Specificity		100%		

DST, drug susceptibility testing; MTB, *Mycobacterium tuberculosis*; NPV, negative productive value; PPV, positive productive value.

found equal to the rates of 100%, 100%, 100% and 100%, respectively (*Table 4*).

Discussion

In this study our objectives were to use cartridge based nucleic acid amplification testing to evaluate patterns of RIF resistance in cases of sputum positive pulmonary TB and to compare between phenotypic and genotypic testing for resistance to RIF in MTB strains of clinically suspected MDR-TB cases.

Multidrug-resistant tuberculosis (MDR-TB) is defined as TB caused by strains of *M. tuberculosis* that are resistant to at least isoniazid and RIF (15). Mono-resistance to RIF is rare; however, 90% of RIF resistant isolates also exhibit resistance to isoniazid. Therefore, the detection of RIF resistance may serve as a surrogate marker for MDR *M. tuberculosis* (16). For RIF resistance detection, Xpert® MTB/RIF provides accurate results and can allow rapid initiation of MDR-TB treatment (17).

In our study, 21 (42%) were RIF resistant, while 29 (58%) were RIF sensitive. This is similar to that reported by Trivedi (18) and Shah (19) where (37.3%) and (37.47%) were resistant to RIF respectively, but lower to the study of Chowgule who reported a very high incidence of RIF resistance of (66.8%) (20). This level of resistance was superior to the study of Rasaki *et al.* (21), Olusoji *et al.* (22), Lawson *et al.* (23), Ganguly *et al.* (6), where (7.2%), (8.6%), (19%), (29.87%) isolates were resistance to RIF respectively and Idigbe *et al.* (24) who reported only 2% of resistance to RIF in Lagos, Nigeria. However, no strain of RIF resistant was reported in the findings of Rasaki *et al.* (21).

There was male preponderance, 15 (71.43%) as against 6 (28.57%) female; this was in concord with the work of Ganguly *et al.* (6) where male subjects had prevalence of 85.71% as against 14.29% of females. Similarly, a European study by Faustini *et al.* (25) observed more drug resistant TB cases among men. This disparity could be due to the fact that male subjects were more exposed to risk factors of TB infection.

In the present study, the distribution according to age showed that the majority of patients with RIF resistance belonged to age group of 31–40 years (n=10; 47.62%) followed by 21–30 and 41–50 years with (n=4; 19.04%) for each age group. This was in concord with the study of Thomas *et al.* (26). In TRC, Chennai, 70% of the drug resistant patients were male and their mean age was 37. In a another study done by Robert *et al.* (27) the age and the sex distribution was similar to the study of Ganguly *et al.* (6) where maximum number of patients with RIF resistance were male and were in the age group of 21–30 years (26.53%) followed by 31–40 years (22.44%).

In our analyzed cohort, 42.85% of cases were retreatment failure cases, Retreatment (Previously CAT II) failure cases were found to be 41.83% among RIF resistant in the study of Ganguly *et al.* (6). In a study done by Sharma *et al.* (28) it was found that 34% of Cat- II failures were drug resistant which is similar to our study. A high prevalence of MDR-TB in Cat-II failure is not restricted to India and has been documented in Vietnam (29), Thailand (30) and Rowanda (31). Retreatment cases smear positive at 4 months were 23.82%, this level was superior to the study of Ganguly *et al.* (6) where retreatment cases smear positive at 4 months found to be 8.16% among RIF resistant cases. 19.05% of cases were retreatment cases smear positive at diagnosis. In studies by Sharma *et al.* (28) and Ganguly *et al.* (6) drug resistance was respectively found in 20% and 22.44% of Retreatment cases at diagnosis which is similar to our study. Ganguly *et al.* (6) found only one resistant case (1.02%) with history of contact with MDR TB. This is consistent with a study done by Singla *et al.* (32) in which only 0.66% of contacts developed MDR-TB. This was lower than what we found in our study where 14.28% patient presented history of contact with MDR-TB.

According to the World Health Organization (WHO) 650,000 people are infected worldwide and 12 million suffer from TB. In Africa, 1.9% of new cases and 9.4% of diagnosed and treated patients are infected by MDR strain (2). The results of this study showed that all strains harboring mutations in *rpoB* were phenotypically MDR-TB strains (resistant to RIF and isoniazid). This was comparable to 77.4% reported by Olusoji *et al.* (22). Few studies had documented the presence of cases infected by MDR strains in Nigeria, with prevalent rates ranging from 4–76.3% (33,34), but was much superior to the results found by Rasaki *et al.* (21) where forty four (31.4%) were positive and to another rates published in previous studies from India (18,35).

Compared to phenotypic DST, the MTB/RIF test correctly identified 21 of 21 patients (100% sensitive) with RIF-resistant bacteria and 29 of 29 (100% specific) with RIF-sensitive bacteria, this is similar to results showed in study conducted in Uganda where 64 smear-positive culture-positive sputa from patients previously treated for TB were tested and the Xpert MTB/RIF test detected nine of nine (100% sensitivity) cases of RIF resistance. RIF resistance was excluded in 55/55 susceptible cases—100% specificity (14). In a recent multicentre (Peru, Azerbaijan, South Africa and India) evaluation study of 1,730 patients with suspected drug-sensitive or multidrug-resistant pulmonary TB, the MTB/RIF test identified 200 of 205 patient (97.6% sensitive) with RIF-resistant bacteria and 504 of 514 (98.1% specific) with RIF-sensitive bacteria (36). In the study of Darwish *et al.* (37) the Xpert MTB/RIF revealed five out of the six cases as being RIF resistant MTB by the conventional method to be RIF resistant MTB with sensitivity 83% and specificity with 100%. Steingart *et al.* (17) emphasized that Xpert can be used as an initial diagnostic test for TB detection and RIF resistance in patients suspected of having TB, MDR-TB or HIV-associated TB.

Conclusions

The high sensitivity and specificity of Xpert MTB/RIF for RIF resistance detection support its use as an initial diagnostic test for RIF resistance. Therefore, implementation of molecular approaches for direct diagnosis of MDR TB, as a part of routine analysis in the laboratories of health care institutions, would be of great benefit in adapting treatment regimens, limiting dissemination of MDR TB strains.

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Footnote

Conflicts of Interest: The authors have no conflict of interest to declare.

Ethical Statement: This study was approved by the institutional ethic review board and informed consent was obtained from all patients.

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